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TITLE: Ocular Safety of Topical Naltrexone

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CONTRACTING ORGANIZATION: Pennsylvania State University
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During the past year we have obtained Institutional Review Board approval from the Hershey Medical Center and DOD for the proposed research. We now are prepared to post notices recruiting research subjects. We are requesting a nine month extension on grant during which to complete our research; however, we are not requesting additional funds.

15. SUBJECT TERMS
Corneal wound healing, corneal abrasion, opioid, opioid antagonist, treatment

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Introduction:

Dr. Sassani and his associates have been funded to perform a Phase I Clinical Trial of Naltrexone dissolved in Vigamox® and applied topically as eye drops preliminary to a therapeutic trial of that medication in the treatment of corneal epithelial defects in diabetic individuals. During the past year, we have obtained Institutional Review Board approval from the Hershey medical Center and the DOD. This approval required more time than anticipated, probably because this is the first time that Naltrexone has been applied topically to the eye even though it is approved for systemic use for other purposes.

Body:

Background: Over the past 18 years, Dr. Sassani has worked with Dr. Zagon's research team delineating the role of the Opioid Growth Regulatory System in corneal epithelial homeostasis and wound healing. We have demonstrated that the native opioid peptide, [Met^5]-enkephalin, termed opioid growth factor (OGF) is a tonically active, receptor mediated, inhibitor of corneal epithelial cell division. Conversely, blockade of the opioid growth factor receptor (OGFr) by the opioid antagonist Naltrexone (NX) up-regulates corneal epithelial cell division. We have demonstrated, further, that NTX accelerates the rate of corneal epithelial wound healing in healthy rodents and rabbits, and reverses the delay in corneal epithelial wound healing characteristic of diabetic keratopathy. No drug-related side effects have been found in animals treated with NTX.

Objective/Hypothesis: Our research suggests that NTX will be useful to expedite corneal epithelial wound healing in normal individuals who suffer ocular trauma, or in individuals with delayed corneal wound healing, such as diabetics. Moreover, our animal experiments indicate that such treatment will be safe as well as effective.

Specific Aims: Phase I Clinical Trials, demonstrating the safety of topically applied NTX in normal volunteers, are requires are required by the FDA before it can before its clinical evaluation relative to expediting human corneal epithelial wound healing can be undertaken. The study we propose has been delineated by the FDA as fulfilling its requirements for the Phase I Clinical Trial. Therefore, its specific aim is to demonstrate in human volunteers the safety of the most concentrations of topical NTX most likely to be used in the clinical setting.

Study Design: Utilizing concentrations of 10^{-6} M, 5×10^{-6} M, 10^{-5} M, and 5×10^{-5} M NTX dissolved in Vigamox® brand of moxifloxacin hydrochloride ophthalmic solution (Alcon), volunteers will receive four drops of the test solution or Ocuflox without NTX over a 24 hour period. They will be examined utilizing clinical observation and standard clinical tests of ocular health within the first 24 hours of drug administration and one week later for evidence of adverse side effects from the medication. At the request of our IRB, an additional research arm was added in which only one drop of experimental drug is given at the lowest of the four concentrations, and followed for one week in the same manner as are the other research subjects.

Impact: Corneal epithelial wounds, whether secondary to Combat trauma or to systemic diseases, such as diabetes mellitus, expose the cornea to significant complications such as infection, ulceration scarring, or even perforation. Expediting corneal epithelial wound healing through the use of topical NTX will reduce the likelihood of such complications in a safe and effective manner using the characteristics of the naturally occurring Opioid Growth Regulatory System.

Public Abstract: The cornea of the eye is the clear tissue through which light enters the front of the eye so that it can be focused as an image on the retina in the back of the eye. The cornea is protected by a thin, five cell thick, skin-like tissue called its epithelium. Breaks in this tissue frequently occur from eye injuries, such as may occur in warfighters from blast-related trauma. These injuries expose the cornea to further damage such as from infections or ulcers, which

can result in scarring and permanent vision loss. Abnormalities of corneal epithelial wound healing, such as occur in individuals with diabetes mellitus, may further inhibit wound healing and increase the likelihood complications from corneal epithelial injuries.

There are multiple treatments for corneal epithelial injuries. Unfortunately, none are uniformly successful, particularly in individuals, such as diabetics. Therefore, there is a need for treatments to enhance corneal epithelial wound healing.

Although we commonly think of opioids as pain medications and consciousness altering drugs, they perform many other bodily functions unrelated to these stereotypes. For the past 18 years, we have studied the role of a naturally occurring Opioid Growth Regulatory system in controlling cell division and wound healing of the corneal epithelium. We have demonstrated that one component of this system, the naturally occurring opioid growth factor (OGF), metenkephalin, decreases the rate of corneal epithelial cell division and wound healing. Conversely, blocking the effect of OGF by applying eyedrops containing the strong blocking agent, Naltrexone (NTX) significantly increases the rate of corneal epithelial cell division and wound healing in normal and in diabetic animals.

Before we can use NTX as a treatment for corneal wounds, we must demonstrate that it is safe to use in patients. The proposed study has been designed in consultation with the U.S. Food and Drug Administration to determine the safety and tolerability of NTX eyedrops in 16 human volunteers. Multiple tests will be performed to document the side effects of this medication if any. The medication is approved to be taken by mouth to treat overdose of substances, such as heroin. It is extremely doubtful, therefore, that the medication will have any adverse side effects when taken in eyedrop form.

NTX has the potential to be a significant improvement in the treatment of corneal injuries in warfighters and in their family members, especially those with abnormalities of corneal wound healing, such as diabetics. The proposed study is a major step in achieving this goal.

Key Research Accomplishments:

As stated in the Introduction, during the past year Dr. Sassani and his associates have obtained Institutional Review Board approval from the Hershey medical Center and the DOD. Included in these reviews was approval of the overall protocol, of the consents for single and multiple drop medication administration, and of the recruiting poster. This approval required more time than anticipated, probably because this is the first time that Naltrexone has been applied topically to the eye, although it is approved for systemic use for other purposes.

Reportable Outcomes:

As yet, there are no reportable outcomes.

Conclusions:

We have completed vital IRB reviews both by the Hershey Medical Center and DOD preliminary to recruiting research subjects (See Appendices A and B). We continue our commitment to the proposed research and look forward to completing it during the next nine months. In order to achieve this goal, we are requesting an extension of the grant period, and a continuation of the present funding for nine months, but are not requesting addition funds over those originally provided by the present award.

References: None

Appendix A

DOD IRB Approval

From: Duchesneau, Caryn L Ms CIV USA MEDCOM USAMRMC

[Caryn.Duchesneau@us.army.mil]

Sent: Sunday, March 14, 2010 11:06 PM
To: Joseph Sassani
Cc: Bennett, Jodi H Ms CIV USA MEDCOM USAMRMC; ayi.ayayi@amedd.army.mil; Phillips, James B Dr DoD Af US USA MEDCOM CDMRP; isz1@psu.edu; dliang@hmc.psu.edu; Brosch, Laura R Dr CIV USA MEDCOM USAMRMC; Duchesneau, Caryn L Ms CIV USA MEDCOM USAMRMC; Wilberding, Julie A Dr CTR US USA MEDCOM USAMRMC; Dustin, Kelly Ms CTR US USA MEDCOM USAMRMC; Drake, Carrie E Ms CTR US USA MEDCOM USAMRMC
Subject: A-15749, HRPO Approval Memorandum (Proposal Log Number PR080379, Award Number W81XWH-09-1-0312)

SUBJECT: Initial Approval for the Protocol, "Phase I Clinical Trial of Topical Naltrexone Applied as Eyedrops," in Support of the Proposal, "Ocular Safety of Topical Naltrexone," Submitted by Joseph W. Sassani, MD, Pennsylvania State University, Hershey, Pennsylvania, Proposal Log Number PR080379, Award Number W81XWH-09-1-0312, HRPO Log Number A-15749

1. The subject protocol was reviewed by the U.S. Army Medical Research and Materiel Command's (USAMRMC) Human Subjects Research Review Board (HSRRB) on 13 January 2010 and granted conditional approval.

2. The revised protocol (dated 22 February 2010) was approved by the Pennsylvania State University College of Medicine (PSU CM) Institutional Review Board (IRB) on 10 March 2010. This protocol has been reviewed and found to comply with the recommendations of the HSRRB and with applicable Federal, DOD, U.S. Army, and USAMRMC human subjects protection requirements.

3. This greater than minimal risk study is approved for the enrollment of 20 subjects.

4. Please note the following reporting obligations:

a. Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments must be submitted with the continuing review report to the HRPO for acceptance.

b. All unanticipated problems involving risks to subjects or others, serious adverse events related to study participation, and deaths related to study participation must be reported promptly to the HRPO.

c. Any deviation to the subject protocol that affects the safety or rights of the subject and/or integrity of the study data must be reported promptly to the HRPO.

d. All modifications, deviations, unanticipated problems, adverse events, and deaths must also be reported at the time of continuing review of the protocol.

e. A copy of the continuing review report approved by the PSU CM IRB must be submitted to the HRPO as soon as possible after receipt of approval. It appears the

next continuing review by the PSU CM IRB is due no later than 31 August 2010.

f. In addition, the current version of the protocol and consent form must be submitted along with the continuing review report and the PSU CM IRB approval notice for continuation of the protocol.

g. The final study report submitted to the PSU CM IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

5. Do not construe this correspondence as approval for any contract funding. Only the
Contracting Officer or Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer
regarding the expenditure of funds for your project.

6. The HRPO point of contact for this study is Kelly Dustin, RN, MS, CCRC, Human Subjects Protection Scientist, at 301-619-2380/Kelly.dustin@us.army.mil <mailto:301-619-2380/Kelly.dustin@us.army.mil> .

CARYN L. DUCHESNEAU, CIP
Chief, Human Subjects Protection Review
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Materiel Command

Note: The official signed copy of this determination memo is housed with the protocol
file at the Office of Research Protections, 504 Scott Street, Fort Detrick, MD 21702.
Signed copies will be provided upon request.

Appendix B

Hershey Medical Center IRB Approval

PENNSTATE HERSHEY
Milton S. Hershey Medical Center

PENNSTATE HERSHEY
College of Medicine

DATE: March 10, 2010

TO: Joseph W. Sassani, MD, MHA

FROM: Bethann Sherrock, BS
IRB Coordinator
Human Subjects Protection Office

RE: IRB Protocol No. 29780 - Phase I Clinical Trial of Topical Naltrexone Applied as Eyedrops

The Human Subjects Protection Office (HSPO) received your February 22, 2010 correspondence with the accompanying documentation regarding the above investigation.

In accordance with Federal guidelines and institutional policy, this issue qualified for review by a designated Institutional Review Board member.

The requested changes outlined in the modification request form (dated 02/22/10) received expedited review and approval was granted on March 10, 2010. This approval includes the following:

- Revised protocol (HMC version date: 02/22/10)
- Revised consent form – single drop and single dosage (dated 02/22/10)
- Revised consent form – multiple drops and multiple dosages (dated 02/22/10)
- Revised advertisement (dated 03/10/10)

Use of copies of the attached, stamped consent forms is required. New form versions supercede all previous versions, which are now invalid for further use. Prior versions should be retrieved and destroyed, with the exception of reference copies retained for your regulatory binder.

If you have any questions, please phone me in the HSPO (ext. 5687). Thank you very much.

BS\